REMARKS

Claims 5, 11, 16, and 23 were previously cancelled. Claims 7-8 have been cancelled in this response. Claims 17-18 and 25 have been withdrawn from consideration due to the Examiner's previous restriction requirement Claims 1-3, 6, and 9 are currently amended. Support for these amendments is found throughout the specification, e.g., at page 3, lines 1-4; page 4, lines 3-6; and page 19, lines 19-21. New claims 26-30 are presented for examination, and they include the requirement that "the indicator activity determined in step b) is increased > 100% relative to the indicator activity determined in step c)." Support for these claims is found throughout the specification, with support for this particular limitation found, e.g., at page 36, line 24 to page 37, line 2. Claims 1-4, 6, 9-10, 12-15, 17-22, 24-25 (and new claims 26-30) are pending in the application.

These claims have been cancelled, withdrawn, or amended without prejudice to, or disclaimer of, the present or original subject matter thereof. Applicants reserve the right to file divisional and continuing applications directed to the subject matter of any claim amended, withdrawn, or cancelled for any reason. By this, Applicants do not acquiesce to the propriety of any of the Examiner's prior rejections and do not disclaim any subject matter to which Applicants are entitled. *Cf. Warner Jenkinson Co. v. Hilton-Davis Chem. Co.*, 520 U.S. 17 (1997).

Applicants thank Examiner Dutt for her time and attention during the telephonic interview held January 11, 2011, and appreciate her acknowledgement and consideration of the presently-filed Supplemental Amendment and Reply.

I. Previous Objections and/or Rejections

Applicants acknowledge the Examiner's withdrawal of the claim rejections under 35 U.S.C. § 103(a). OA at 2-3. Applicants further acknowledge the Examiner's withdrawal of the claim rejections under 35 U.S.C. § 112, second paragraph. OA at 3.

II. Claim Rejections – 35 U.S.C. § 112 – Scope of Enablement

The Examiner has maintained the rejection of dependent claims 7-10 and independent claim 1 for the following reason:

> [T]he specification, while being enabling for a method of identifying a candidate compound for enhancing cyclic AMP response element binding protein (CREB) pathway function by contacting host cells/cells of neural origin with a test compound and forskolin, wherein the indicator activity/CREB dependent gene expression in cells treated with forskolin and test compound is significantly increased versus that observed with cells plus forskolin alone, does not reasonably provide enablement for the identification of a candidate compound following the same steps resulting in **any difference** in CREB dependent gene expression between the groups as stated above (see claims 7-10, particularly 7(m)) (emphasis added).

OA at 3-4.

According to the Examiner, "amending claim 7(m) to recite 'significant increase' would overcome this rejection." OA at 5 (emphasis in original). In response, Applicants have cancelled claims 7 and 8 and amended claim 9 so that it (and claim 10) now depend directly or indirectly from claim 1. Accordingly, Applicants respectfully assert that this rejection is moot and should be withdrawn.

III. Claim Rejections – 35 U.S.C. § 112, Second Paragraph

The Examiner has rejected claims 7-10 as being indefinite. OA at 6. According to the Examiner, "[c]laim 7(m) is vague and unclear for reciting the limitation 'a difference' because '[t]he instant specification teaches statistically significant increased gene expressions" and "[i]t is not clear if the difference should be significant or can be non-significant as well." OA at 6.

As just discussed, claims 7-8 have been cancelled and claims 9-10 now depend directly or indirectly from claim 1. Accordingly, Applicants respectfully assert that this rejection is moot and should be withdrawn.

IV. Claim Rejections – 35 U.S.C. § 103 -- Obviousness

The Examiner has rejected claims 1, 3-4, and 6 under 35 U.S.C. §103(a) as being unpatentable over Ying et al. ("Ying") in view of Tully et al. (WO 96/11270) and further in view of Shoemaker et al., OA at 6-11 ("Shoemaker"). Applicants respectfully traverse.

In proceedings before the USPTO, "the Examiner bears the burden of establishing a *prima facie* case of obviousness based on the prior art."[1] "To establish a *prima facie* case of obviousness, the Examiner must meet four conditions:

First, the Examiner must show that the prior art suggested to those of ordinary skill in the art that they should make the claimed composition or device or carry out the claimed process. This requires that "[a] prior art reference must be considered in its entirety, i.e., as a whole, including portions that would lead away from the claimed invention."[2]

Second, the Examiner must show that the prior art would have provided one of ordinary skill in the art with a reasonable expectation of success. Both the suggestion and the reasonable expectation of success must be adequately founded in the prior art and not in an applicant's disclosure.

Third, when determining whether a claim is obvious, an examiner must make "a searching comparison of the claimed invention – including all its limitations – with the teaching of the prior art."[3] Thus, "obviousness requires a suggestion of all limitations in a claim."[4]

Fourth, if an obviousness rejection is based on a combination of prior art references, the Examiner must show a suggestion, teaching, or motivation ("TSM test') to combine the prior art references.[5] Following the Supreme Court's decision in *KSR v. Teleflex*,[6] the TSM test must be applied flexibly to accord with the Court's approach of *Graham v. Deere.*[7] A "flexible TSM test remains the primary guarantor against a non-

---

[1] *CFMT, Inc. v. Yieldup Int'l Corp*., 349 F.3d 1333, 1342 (Fed. Cir. 2003); *See In re Bell,* 991 F.2d 781, 781 (Fed. Cir. 1993) ("A prima facie case of obviousness is established when the teachings from the prior art itself would appear to have suggested the claimed subject matter to a person of ordinary skill in the art.").

[2] M.P.E.P. § 2141.02 (VI) (July 2010) (citing *W.L. Gore & Associates, Inc. v. Garlock, Inc*., 721 F.2d 1540, (Fed. Cir. 1983)).

[3] *In re Ochiai*, 71 F.3d 1565, 1572 (Fed. Cir. 1995) (emphasis added)

[4] *CFMT, Inc. v. Yieldup Intern. Corp*., 349 F.3d 1333, 1342 (Fed. Cir. 2003) (citing *In re Royka*, 490 F.2d 981, 985 (CCPA 1974).

[5] *In re Dembiczak*, 175 F.3d 994, 998 (Fed. Cir. 1999).

[6] *KSR Int'l Co. v. Teleflex, Inc*., 550 U.S. 398, 418 (2007).

[7] *Graham v. John Deere*, 383 U.S. 1, 17-18 (1966).

statutory hindsight analysis" in obviousness cases,[8] capturing the important insight that "a patent composed of several elements is not proved obvious merely by demonstrating that each of its elements was, independently, known in the prior art."[9]

The Examiner provides the following descriptions of the Ying et al., reference:

> Ying et al., teach that host cells (Calu-6 or human lung cancer cells) were transiently transfected using plasmids comprising the HREN promoter having the consensus CRE sequence (e.g. 900L, 900CRE, etc.) (Table 1; Figure 1), luciferase indicator gene, and expression vector encoding the CREB-1 transcription factor (abstract) and contacted with forskolin (Materials and Methods, page 2413, col. 2, para 2). The reference further teaches that the luciferase activity elicited by cells transfected with reporter constructs such as 900CRE, and contacted with CREB expression vector along with forskolin is significantly increased with respect to cells without the CREB expression vector. Additionally, the cells not treated with forskolin and CREB expression vector are not significantly different than cells in contact with CREB expression vector alone (Figure 6A).

OA at 7-8.

The Examiner acknowledges, however, that Ying does not teach either "the screening of a plurality of compounds that would enhance CREB function" or "repeating the method steps with a range of concentrations of the test compound." OA at 8. Instead the Examiner asserts that alleged teachings in Tully et al., and in Shoemaker et al., cover these deficiencies of Ying:

> Tully et al., teach screening assays of pharmaceutical drugs for enhancing long-term memory by activating CREB or CREB isoforms (page 4, para 4; page 5, para 2).
>
> Shoemaker et al., teach drugs for screening assays for different tumor types including neuroblastoma cells (page 2149, Table 3). Shoemaker et al., also teach that after the primary or initial screening steps of identifying test compounds, dose response assays involving 10-fold dilutions (or different concentrations) of test compound was performed (page 2146, col. 1, Drug Treatment, Materials and Methods). The reference further teaches that the complete evaluation of active compounds will involve 5-dose response experiments (i.e. will include four different concentrations as in instant claim 6) using the assay steps (or repeating the steps

[8] *Ortho-McNeil Pharma v. Mylan Labs.*, 520 F.3d 1358, 1364 (Fed. Cir. 2008).

[9] *KSR* at 418.

> done with the original concentration), for determining the minimum effective concentration of the test compound (page 2150, col. 1, para 2).

OA at 8-9.

As set forth below, this obviousness rejection is insufficient because the combination of references fails to teach or suggest all elements of the claims, and because Ying et al. and Shoemaker teach away from the presently-claimed methods.

A. The cited combination of references fails to teach or suggest a "suboptimal dose of a CREB function stimulating agent"

The Examiner states that "[t]he claims are directed to a method of identifying candidate compounds for enhancing CREB pathway function (i) by contacting host cells comprising an indicator gene linked to a CRE promoter with a test compound and *CREB function stimulating agent (forskolin)* . . ." OA at 7 (emphasis added).

This statement is incomplete, however, because it fails to acknowledge that the rejected claims all require contacting host cells with a *suboptimal* dose of a CREB function stimulating agent (forskolin). As described in the instant application, a suboptimal dose of a CREB function stimulating agent allows reliable detection and measurement of effects of cognitive enhancers:

> By suboptimal dose of CREB function stimulating agent is meant that amount, or dose, of CREB function stimulating agent that is required to stimulate (induce) CREB pathway function to a level that is above endogenous (basal) levels, such that a further statistically significant increase in CREB pathway function due to induction by a cognitive enhancer can be measured and the measurement is not attributable to natural cellular fluctuations or variations as a consequence of natural cellular fluctuations . . . The suboptimal dose of CREB function stimulating agent will be any concentration yielding (1) 50% or less maximal indicator activity and (2) an indicator activity above natural cellular fluctuations.

Application, p. 19, l. 22 to p. 20, l. 16.

The requirement for a suboptimal dose also underscores a guiding principle set forth in the instant application: to identify compounds "that do not enhance CREB function on their own but rather after co-stimulation with forskolin, an activator of adenylyl cyclase." Application, p. 36, ll. 7-16.

The Examiner's reliance on Ying as teaching "host cells that were . . . contacted with forskolin" (OA at 8-9) is therefore deficient because the Examiner has not provided a basis in Ying for host cells contacted with a *suboptimal* dose of forskolin. Nor *can* Ying provide such a basis: the studies in Ying are directed to quantitative studies of "the DNA sequence and transcription factor requirements for cAMP-induced transactivation of the human renin [HREN] promoter using Calu-6 cells that express human mRNA endogenously." Ying, p. 2412, col. 1. The results reveal, for example, that "[f]orskolin treatment alone only caused a 2-3 fold activation of the *HREN* promoter in Calu-6 cells, but nearly a 10-fold activation in JED-3 cells, which do no express rennin but are highly responsive to cAMP." *Id.* Such quantitative comparisons logically depend on full induction of cAMP signaling through optimal amounts of forskolin, and certainly do not teach or suggest *suboptimal* amounts, as claimed.

More generally, the studies in Ying are focused on components acting *downstream* of cAMP, and they include the use of "[e]xpression vectors encoding the CREB-1 transcription factor, a dominant negative mutant form of CREB-1, and the catalytic subunit of protein kinase A (PKA) . . . to assess transcription factor requirements mediating the cAMP response." Ying, p. 2412 col. 1. This downstream focus further underscores the need for peak levels of cAMP – and hence a saturating dose of forskolin – at the top of the signaling cascade. In this regard, the concentration of forskolin is not manipulated in any experiments in Ying et al., but is maintained at an invariant concentration (10 μM). (See Materials and Methods, *Transfections and Luciferase Assays*, p. 2143, col. 2) In sum, the Examiner has not provided the requisite teaching or suggestion in Ying for a *suboptimal* concentration of CREB function stimulating agent (forskolin), nor *can* such a teaching or suggestion be found.

Moreover, this deficiency is not overcome by the Tully et al., and Shoemaker references: The Examiner relies on Tully et al., for the general teaching of screening assays based on activating CREB or CREB isoforms. But Tully et al., do not disclose or suggest using a *suboptimal* concentration of CREB function stimulating agent (forskolin) for use in the methods of the present invention, and the Examiner's citations to this reference are unavailing. The Examiner's citation to page 4, paragraph 4, for example, is directed to a behavioral assay for assessing a drug, such as one "altering the induction or activity of repressor and activator isoforms of dCREB2," but it says

nothing about using a suboptimal dose of a CREB function stimulating agent. Similarly, the Examiner's citation to page 5, paragraph 2 is directed to screening assays based on modulating the relative level of CREB activator and repressor isoforms and says nothing about using a suboptimal dose of CREB function stimulating agent.

Also deficient is Shoemaker, which is directed to the "applicability of a human tumor colony-forming assay . . . in terms of feasibility, validity and potential for drug discovery." Shoemaker, p. 2145, col. 1. However, the primary or initial screening step based on the tumor colony-forming assay does not teach or suggest using a second modulatory agent, such as forskolin – much less using a *suboptimal* dose of such an agent.

Ying therefore fails to teach or suggest administering a suboptimal dose of a CREB function stimulating agent, and Tully et al., and Shoemaker fail to correct this important deficiency. On this basis alone, the cited combination of references fails to teach or suggest all limitations of the claimed inventions. Accordingly, it is respectfully asserted that the Examiner has not – and can not – establish a *prima facie* case of obviousness and Applicants respectfully request reconsideration and withdrawal of the present rejection.

B. <u>The cited combination of references teaches away from "contacting cells of neural origin."</u>

As amended, independent claim 1 (and dependent claims 2, 4, and 6) requires the element of "contacting cells of neural origin." The cells of neural origin are further limited to neuroblastoma cells in dependent claim 3, to neurons in dependent claim 9, and to primary hippocampal neurons in dependent claim 10.

The primary reference Ying does not teach or suggest use of cells of neural origin. Instead it is directed to studies of the human renin promoter in a renin-expressing, lung carcinoma cell line (Calu-6)[10] and a cAMP-responsive, placental choriocarcinoma cell line (JEG-3).[11] Not only are the studies in Ying limited to these two cell-lines; they also show unpredictability of these two cell-lines. For example,

[10] *See, e.g.*, http://www.cell-lines-service.de/content/e143/e1780/e1176/index_eng.html
[11] *See, e.*g., http://www.cell-lines-service.de/content/e143/e1778/e1312/index_eng.html

CREB-1 increases 900CRE activity 7-fold in Calu-6 cells—but has no effect on 900CRE activity in JEG-3 cells. Conversely, CREB-1 has little or no effect on 900CRE activity in forskolin-treated Calu-6 cells—although it may slightly increase 900CRE activity in forskolin-treated JEG-3 cells. Ying therefore fails to teach or suggest contacting cells of neural origin – much neuroblastoma cells.

Moreover, Tully et al., and Shoemaker fail to overcome this deficiency, as neither reference teaches or suggests contacting cells of neural origin: With respect to Tully et al., the Examiner's citation to page 4, paragraph 4 is – as noted above – directed to a *behavioral* assay for assessing a drug, and it says nothing about contacting cells of neural origin – much less contacting such cells with a CRE reporter construct and a *suboptimal* dose of a CREB function stimulating agent. Also unavailing is the Examiner's citation to page 5, paragraph 2, which is directed to screening assays, based on modulating CREB isoforms, but it too says nothing about contacting cells of neural origin.

With respect to Shoemaker, the Examiner states that "Shoemaker teaches drugs for screening assays for different tumor types including neuroblastoma cells." OA at 8. A closer look at Shoemaker, however, reveals that it actually teaches away from drugs for screening assays in neuroblastoma cells, as well as neural cells generally.

In particular, Shoemaker relates to the applicability of a colony formation assay as a screen for cancer drugs directed to particular tumor types. Table 3 summarizes the "culturability" of 38 different tumor types,[12] and it includes the one and only mention of neuroblastoma cells. Shoemaker, p. 2147, col. 1. But Table 3 reveals that all attempts to culture neuroblastomas failed; in every case, the cells did not reach the minimum growth requirements necessary to be considered an evaluable assay. Shoemaker, p. 2147, col. 2.

More generally, Shoemaker teaches that "[c]ertain tumor types such as head and neck tumors, lymphomas, and sarcomas performed very poorly" and that "[t]his presumably reflects a requirement for growth factors or nutrients not present in the culture medium." Shoemaker, p. 2151, col. 2. Shoemaker then concedes that '[i]n recognition of these problems, we have limited drug-screening studies to a subset of

[12] See Shoemaker, p. 2148, col. 1.

tumors (breast, colorectal, kidney, lung, melanoma, and ovarian tumors) which are both available in adequate number and tend to perform well in the assay." *Id.* None of these are cells of neural origin. Corroborating this view, Table 3 shows that all attempts to culture nervous system tumors also failed and that attempts to culture brain tumors fared worse than that for head/neck tumors, yielding the same low percent of evaluable assays but fewer colonies. Shoemaker, p. 2147, col. 1.

Shoemaker therefore teaches away from the use of neuroblastoma cells – and neural cells generally – in the drug screening assays. Accordingly, one skilled in the art would *not* combine Shoemaker with Ying and Tully et al. to arrive at the claimed screening methods.

C. The cited combination of references fails to teach or suggest step g) of claim 1

Step g) of claim 1 includes two requirements for selecting a test compound: (i) a significant increase of indicator activity in host cells contacted with test compound and forskolin relative to host cells contacted with forskolin alone; and (ii) no significant change of indicator activity in host cells contacted with a test compound alone relative to host cells alone.

As alleged support for these two limitations, the Examiner relies on Figure 6 of Ying:

> The reference further teaches that the luciferase activity elicited by cells transfected with reporter constructs such as 900CRE, and contacted with CREB expression vector along with forskolin is significantly increased with respect to cells without the CREB expression vector.
>
> Additionally, the cells not treated with forskolin and CREB expression vector are not significantly different than cells in contact with CREB expression vector alone (Figure 6A).

OA at 8.

This interpretation is faulty for several reasons. At the outset, Figure 6 of Ying provides six sets of experimental data, encompassing the analysis of three different constructs in two different cell-lines. However, only one data set – the 900CRE construct in Calu-6 cells – appears to support the Examiner's position. This selective

reliance therefore is to the exclusion of all contradictory data in Figure 6. This failure to consider Ying as a whole is improper as a matter of law.[13]

Furthermore, this selective view fails to acknowledge disclosures in the Ying that teach away from the claimed methods. For example, the 900CRE data in Figure 6 that the Examiner selectively relies upon is cell-type specific. In addition, the effect of CREB on forskolin-induced activity of 900CRE in Calu-6 cells is less than two-fold. This effect is far from robust: In fact, the abstract states that "over-expression of CREB-1 did *not* significantly enhance forskolin-induced human renin transcriptional activity." Indeed, there is no evidence that CREB-1 would have *any* effect with co-stimulation of a *suboptimal* dose of forskolin. In this regard, the studies shown in Figure 7 reveal that Calu-6 cells are deficient in components of cAMP signaling cascade. Given these limitations and restrictions, one skilled in the art would not recognize the applicability of Ying to forskolin-based screening for enhancers of CREB pathway function recited in the instant claims.

Ying therefore does not teach or suggest step g) of the rejected claims. In addition, the Tully et al., and Shoemaker references do not overcomes this deficiency: Neither reference teaches or suggests comparative studies of CRE-based reporters in transfected cells.

In sum, because the cited combination of references fails to teach or suggest all limitations of the claimed invention – indeed they teach away – the Examiner has not and can not establish a *prima facie* case of obviousness. Accordingly, Applicants respectfully request that the Examiner reconsider and withdraw the rejection of the under 35 U.S.C. §103(a).

V. New Claims 26-30

Presented for examination are independent claim 26 and dependent claims 27-30. Claim 26 is identical to the last version of claim 1 before the current amendment – with one additional limitation: Claim 26 sets a minimal increase of $\geq$ 100% for the indicator activity determined in step b) relative to the indicator activity determined in step c). In

[13] M.P.E.P. § 2141.02 (VI) (July 2010) (citing *W.L. Gore & Associates, Inc. v. Garlock, Inc.*, 721 F.2d 1540, (Fed. Cir. 1983)).

other words, claim 26 requires that a candidate enhancer compound produces at least a 100% increase in indicator activity in forskolin-treated cells relative to control cells treated with forskolin alone. As discussed above, Ying shows little or no effect of CREB-1 on 900L activity in forskolin-treated Calu-6 cells. In Ying, CREB-1 does appear to produce a slight increase in 900CRE activity in forskolin-treated Calu-6 cells, but even if this increase is significant, it is visibly less than 100 %. In addition, neither Tully et al., nor Shoemaker teach or suggest this limitation, which is supported by the specification, for example, at page 36, line 24 to page 37, line 2, which discusses such parameters for a primary screen.

CONCLUSION

Applicants have properly and fully addressed each of the Examiner's grounds for rejection. Applicants submit that the present application is now in condition for allowance. If the Examiner has any questions or believes further discussion will aid examination and advance prosecution of the application, a telephone call to the undersigned is invited. If there are any additional fees due in connection with the filing of this amendment, please charge the fees to undersigned's Deposit Account No. 50-1067. If any extensions or fees are not accounted for, such extension is requested and the associated fee should be charged to our deposit account

Respectfully submitted,

/djpelto Reg. No. 33754/

Date: January 12, 2011

Don J. Pelto
Reg. No. 33,754

Sheppard Mullin Richter & Hampton LLP
1300 I Street NW
Eleventh Floor East
Washington, D.C. 20005
Tel: (202) 772-5362
Fax: (202) 312-9415